Public & philanthropic financial contribution to the development of new drugs

Methodology & 3 Case Studies

Ludwig Boltzmann Institut
Health Technology Assessment

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Zusammenfassung

Hintergrund

Der Begriff „Access to Medicines“ war bis vor wenigen Jahren mit der Diskussion um günstigere (generische) lebenswichtige Medikamente (HIV, Tuberkulose, etc.) in Entwicklungsländern verbunden. Seit einiger Zeit befassen sich nun auch westliche Länder und Institutionen (OECD, Europäische Commission, etc.) mit dem „Zugang zu Medikamenten“, um den „nicht-nachhaltigen“ Medikamentenpreisen entsprechende Lösungen entgegenzusetzen.

intensive internationale Diskussion zu „Access to Medicines“ (Zugang zu Medikamenten) wegen „nicht-nachhaltigen“ Medikamentenpreisen

Die Ausgaben für Forschung & Entwicklung (F&E) werden von den Herstellern zumeist als Begründung verwendet, um die hohen Preise zu rechtfertigen. Die eigentliche – ressourcenaufwändige und risikoreiche – Grundlagenforschung findet aber überwiegend im öffentlichen Sektor (in Universitäten und entsprechenden öffentlich-finanzierten Forschungseinrichtungen) statt. Wenig publiziertes Wissen zu öffentlichen Ausgaben liegt hingegen bislang vor. Das Projektziel ist, die öffentlichen Beiträge zu Arzneimittelforschung und -entwicklung zu erheben und damit einen Beitrag zur Diskussion um „Return on Investment of Public Investment“ zu leisten.

F&E Ausgaben von Herstellern als Begründung für hohe Preise
aber: hohe öffentliche Grundlagenforschung als Basis für Medikamentenentwicklung

Methode

Das Projekt erfolgte zwei-stufig: In Phase 1 wurde an der Entwicklung einer Methode (Suchstrategie und Quellen) gearbeitet, um den Beitrag der öffentlichen Forschungsförderung bei der Entwicklung neuer Medikamente systematisch zu ermitteln. In *Phase 2 wurde die Methode* des in Phase 1 entwickelten Analyseansatzes anhand von drei ausgewählten Arzneimitteln pilotiert. Für die Pilotierung wurden pädiatrische Orphan Drugs (Spinraza®, Brineura®, Crysvita®), die 2017 von der Europäischen Arzneimittel-Agentur (EMA) zugelassen wurden, ausgewählt.

zwei-stufiges Projekt
Phase 1: Methodenentwicklung
Phase 2: Pilotierung an 3 Orphan Drugs

Ergebnisse

Ergebnis Methode: ein mehrstufige Suchprozess wurde als Leitfaden für Suchen nach öffentlichen (und philanthropischen) Forschungsförderungen entwickelt:

Ergebnis Methode:

- *Schritt 1:* Identifikation aller generischen wie molekularer Namen und Begriffe des Arzneimittels entlang des gesamten F&E Prozesses in Datenbanken (DrugBank, ChEMBL, Therapeutic Target Database).
- *Schritt 2:* Systematische Suche nach Informationen zum Entwicklungspfad vor Zulassung und entsprechenden Forschungsförderungen wie Patentierungen in den Entwicklungsschritten in multiplen Datenbanken und Studienregistern (Orphanet; Studienregister: WHO international trials registry, US-Clinical Trials.Gov; EU clinical trials registry; Patent-Datenbanken: FDA orange book, Espacenet, Health Canada Patent Database; Zulassungsinstitutionen: FDA, EMA; Bibliographische Datenbanken: PubMed, Google).
- *Schritt 3:* Systematische Suche nach Forschungsförderungen (NIH-REPORTER-Database, CORDIS, IMI, EDCTP, diverse philanthropische Quellen, etc.).

mehrstufiger Suchprozess in verschiedenen Datenbanken

Ergebnis Pilotierung

Ergebnis Pilotierung: die Suchstrategie wurden an drei pädiatrische Orphan Drugs pilotiert, wobei der Zeitraum zwischen der Identifikation des Moleküls/Wirkmechanismus/Genidentifizierung und des Jahres der Zulassung als Zeitrahmen angenommen wurde:

Nusinersen/Spinraza®

- *Nusinersen/Spinraza®:* mithilfe eines Dokuments des National Institute of Neurological Disorders and Stroke (NINDS) konnte die Stufen der Entwicklung von Nusinersen detailliert nachverfolgt werden. Es wurden > 40 öffentlich, aber auch philanthropisch geförderte Projekte identifiziert. Insgesamt wurden Förderungen für SMA F&E in der Höhe von € 165 Million (davon € 20 Million direkt Produkt-bezogen) gefunden.

Cerliponase alpha/ Brineura®

- *Cerliponase alpha/Brineura®:* mithilfe eines Dokuments des National Institute of Neurological Disorders and Stroke (NINDS) konnte der Zeitpunkt der frühen Entwicklung identifiziert werden. Es wurden > 20 öffentlich sowie einige philanthropisch geförderte Projekte identifiziert werden. Es konnten öffentliche Forschungsfördersummen gefunden werden (nur Produkt-bezogen € 31 Million) aber keine philanthropische Summen.

Burosumab/Crysvita®

- *Burosumab/Crysvita®:* Aufgrund der Entwicklung des Wirkstoffs in Japan konnten keine/kaum Informationen in englischer Sprache gefunden werden. Es wurden viele öffentlich sowie einige philanthropisch geförderte Projekte identifiziert, jedoch nur wenige konkrete Summen (€ 26 Million in englischen-sprachigen Quellen, vor allem in der Grundlagenforschung).

Schlussfolgerung

Mangel an Transparenz bei Quellen
Komplexität der Suchfilter
weitere Pilotierungen mit Verfeinerung der Suchstrategie geplant

Die Recherchen zu öffentlichen und philanthropischen F&E Förderungen erwiesen sich als sehr zeitaufwändig. Hindernisse waren ein Mangel an Transparenz in den diversen Datenbanken und Quellen und/oder Komplexität der Suchfilter (Eingrenzung des Suchzeitraums und Unterscheidung zwischen Grundlagenforschung und Forschung zur Produktentwicklung) sowie Sprachbarrieren. Die Suchstrategien mussten individuell angepasst werden, die Ergebnisse sind sehr unterschiedlich. An weiteren Pilotierungen wie einer Verfeinerung der Suchstrategie wird gearbeitet.

Executive Summary

Background

intensive international discussion on "access to medicines" caused by "unsustainable" drug prices

The term "access to medicines" was until a few years ago associated with the discussion surrounding cheaper (generic) vital drugs (HIV, tuberculosis, etc.) in developing countries. For some time, Western countries and institutions (OECD, European Commission, etc.) have also begun to focus on "access to medicines" in an attempt to counteract "unsustainable" drug prices.

manufacturer argument: R & D expenditures as justification but: high public contributions to R&D

Expenditure on research and development (R & D) is mostly used by manufacturers as a justification for high prices. The real – resource-consuming and high-risk – basic research takes place mainly in the public sector (in universities and corresponding publicly funded research institutions) instead. Little publicized knowledge on public spending, however, exists so far. The project objective is to collect information on public contributions to drug research and development and thus contribute to the discussion on "Return on Investment of Public Investment".

Methods

2 stage project: phase 1: development of methodology phase 2: piloting methodology in 3 orphan drugs

The project was carried out in two stages: in Phase 1, a methodology (search strategy and sources) was developed to systematically identify the contribution of public research funding to the development of new drugs. In Phase 2, the methodology of the Phase 1 analytical approach was piloted using three selected drugs. Pediatric Orphan Drugs (Spinraza®, Brineura®, Crysvita®), which were approved by the European Medicines Agency (EMA) in 2017.

Results

results methods:

Results on Methods: A multi-level search process was developed as a guide to searches for public (and philanthropic) research funding:

multi-level search strategy

- *Step 1:* Identification of all generic and molecular names and terms of the drug along the entire R & D process in databases (DrugBank, ChEMBL, Therapeutic Target Database).
- *Step 2:* Systematic search for pre-marketing pathway information, and related research funding such as patenting, using multiple databases and trial registries (Orphanet, WHO Clinical Trials.Gov, Patent Databases: FDA Orange Book, Espacenet, Health Canada Patent Database; Regulatory Institutions: FDA, EMA; Bibliographic Databases: PubMed, Google).
- *Step 3:* Systematic search for corresponding research funding amounts (NIH-RePORTER-Database, CORDIS, IMI, EDCTP, various philanthropic sources, etc.).

results of pilots

Results of pilots: the search strategy was piloted on three paediatric orphan drugs, taking the period between the identification of the molecule/ mechanism of action/gene and the date of market authorisation as the relevant time frame:

Nusinersen/Spinraza®

- *Nusinersen/Spinraza®:* Nusinersen's scientific developmental stages were identifiedusing a document from the National Institute of Neurological Disorders and Stroke (NINDS). In total we were able to identify > 40 publicly but also philanthropically funded projects. In total, subsidies for SMA R & D in the amount of € 165 million (of which € 20 million were product-related) were found.

Cerliponase alpha/ Brineura®

- *Cerliponase alpha/Brineura®:* Using a document from the National Institute of Neurological Disorders and Stroke (NINDS), it was possible to identify the time of early scientific development. We could identify > 20 public and some philanthropic funded projects from this date, but the philanthropic contribution was harder to quantify. We put a conservative estimate of public funding (i.e. national and international funding, excluding charities) for this product at € 31 million.

Burosumab/Crysvita®

- *Burosumab/Crysvita®:* Regarding the development of the active ingredient in Japan, little/no information could be found in English. Many public and some philanthropically funded projects have been identified. The sum of publically funded, mostly basic research, is estimated at € 26 million (English-language sources only).

Conclusions

lack of transparency of sources + complexity of search filters
further piloting with refinement of search strategy planned

The research on public and philanthropic R & D funding proved to be very time consuming. Obstacles were a lack of transparency in the various databases and sources and/or complexity of the search filters (narrowing the search period and distinguishing between basic research and product development research) and language barriers. The search strategies had to be adapted individually, the results are very different. Further piloting such as a refinement of the search strategy is underway.

1 Methodology

1.1 Introduction

methodology based on published work

This document describes the methodology that will be implemented to assess the public or philanthropic contribution to the drug discovery and development process, following on from published work in this area [1-5].

focus: basic & early-stage research, early clinical trials

The focus is on basic and early-stage research as well as early clinical trials. This includes what is termed step 1 of the drug development process, known as discovery and development, and step 2, termed preclinical research. There may also be phase 0 clinical trials (exploratory studies that often use only a few small doses of a new drug in a few patients, designed to speed up and streamline the drug approval process) as well as phase 1-3 clinical studies up to the date of market authorisation, which form part of step 3, clinical research[1, 2].

1.2 Case studies

3 case studies – then refinement or affirmation of methodology

Up to 3 case studies are planned initially, before refinement or affirmation of methodology. Products will be chosen using the EMA list of new active substances relating, in the first instance, to the area of orphan medicine, preferably paediatric-relevant products. 35 new active substances were recommended for approval by EMA in 2017, 13 of which were orphan products: Bavencio, Besponsa, Lutathera, Rydapt, Zejula (all cancer products); Prevymis (infections); Crysvita, Xermelo (endocrinology); Brineura, Oxervate, Spinraza (neurology), Refixia (haematology), Alofisel (hepatology/gastroenterology). Four of these orphan products were declared by the EMA to be medicines for children representing an outstanding contribution to public health: Brineura, Spinraza, Alkindi and Crysvita. These four products will constitute the first case studies.

selection of products: approved 2017 orphan drugs, paediatrics

Brineura, Spinraza, Crysvita

After these have been completed, further suitable case studies will be determined and will potentially include non-orphan and non-paediatric products.

extraction of information

The following information will be extracted from the identified funding organisations (as far as possible): study title; date of funding; amount of funding; stage of development/content of project; lead institution; principal investigator; co-operating institutions. The results will be presented in tabular form.

[1] https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process

[2] https://www.ecmcnetwork.org.uk/what-are-clinical-trials

Inclusion and exclusion criteria

academic papers, grey literature & online information

on public or philanthropic funding

before marketing authorisation

All academic papers, grey literature and online information relating to the development of the drug in question that took place before the date of marketing authorisation will be considered relevant, if there is any mention of public or philanthropic funding. There is no restriction relating to the type of article (e.g. trial or review) or the quality of the publication. The aim is to develop a picture of the development of the drug and for that reason a broad definition of potential relevant information is used. When a product has multiple indications, public contributions to all indications prior to date of market approval will be included.

1.3 Definition of drug terms

1st step: identification of (non-proprietary, chemical) drug names

The first step is to determine all the names under which the drug was known during the development, including the relevant molecular terms. For this purpose, the following databases are searched and names relating to the international non-proprietary name, chemical name and mechanism action of the product will be documented.

Table 1.3-1: Databases for searches of drug-relevant information

DrugBank https://www.drugbank.ca/	This is a comprehensive source of bioinformatic and chemical information, combining detailed data on drugs (e.g. synonyms, chemical, pharmacological and pharmaceutical data) with detailed information on target connections (targets) e.g. sequence, structure, metabolic pathways.
ChEMBL https://www.ebi.ac.uk/chembl/	Database of bioactive molecules with drug properties that includes synonyms, brand names, generic names and pre-commercial company names, as well as MeSH terms related to NCBI Query Translation.
Therapeutic Target Database (TTD) http://bidd.nus.edu.sg/group/cjttd/	Database that provides information about known and researched therapeutic proteins and nucleic acid targets, the targeted disease, pathway information and the corresponding drugs for each of these targets. This database also contains links to relevant databases containing information on target function, sequence, 3D structure, ligand binding properties, enzyme nomenclature and drug structure, therapeutic class, clinical development status.

1.4 Search strategy

2nd step: systematic search in multiple databases

databases:

Orphanet: resources on rare diseases and drugs

A combination of search strategies is used to generate a picture of the product and the development path it underwent, using the product-related search terms identified in the previous stage. These searches are detailed below:

- Orphanet https://www.orpha.net/consor/cgi-bin/index.php?lng=DE: for orphan drugs. This is a database that brings together resources on rare diseases and drugs for the treatment of rare diseases (so-called orphan drugs) to improve their diagnosis and treatment. Orphanet was initiated in 1997 by the French Ministry of Health and the Institut national de la santé et de la recherche médicale (INSERM) and is now run by a consortium of European partner countries under French leadership and with support from the European Union.

clinical trials registries

The following three databases are searched for information on clinical trials prior to marketing authorisation:

for trials prior to marketing authorisation

- WHO international trials registry: http://apps.who.int/trialsearch/ US-Clinical Trials.Gov: https://www.clinicaltrials.gov/ and EU clinical trials registry/EudraCT: https://www.clinicaltrialsregister.eu/ctr-search/search. Also clinical study registries of relevant pharmaceutical companies are checked, where available: e.g. **Fehler! Hyperlink-Referenz ungültig.**. The aim of searching these clinical trials databases is primarily to find potentially relevant clinical studies.

patent databases

- Patent database searches are conducted to try to ascertain whether universities, research groups or other organisations aside from the pharmaceutical company are listed. The following databases for the USA and Europe will be used: FDA orange book US PTO : https://www.accessdata.fda.gov/Scripts/cder/ob/index.cfm; https://www.uspto.gov/, the Espacenet patent database: https://worldwide.espacenet.com/ and Health Canada Patent Database: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/patent-register.html.

for patents of public bodies

further patent identification options

- Also check the following for information on patents:
  - Medicines Patent Pool Patent Search: https://www.medspal.org/,
  - Pat-informed database: https://www.wipo.int/pat-informed/en/,
  - U.S. Patents with US Government Rights Declared http://drugdatabase.info/databases/us-patents-government-rights-declared/
  - EDGAR Company Filings to identify company records which lists relevant patent numbers for the products: https://www.sec.gov/edgar/searchedgar/companysearch.html (in particular the 10-K which sometimes lists patents)

multiple sources

drug approval institutions

- Websites of product approval organisations
  - FDA Label: https://www.drugbank.ca/drugs/DB13173 includes drug information (description, pharmacology, clinical studies, indications and contraindications, ...),
  - EMA label https://www.ema.europa.eu/en/medicines/human/ which similarly provides drug information (see particularly the EMA assessment report).

FDA
EMA

pharmaceutical companies

- Websites of the pharmaceutical companies: The website of the pharmaceutical company marketing the product is searched for relevant information; including a check of the annual reports available online (is there any mention of R&D expenses or licenses/co-operations regarding external laboratories/universities?)

R&D co-operation and expenses

- Bibliographic database:
  - PubMed is searched using an ontology of drug names restricted to publications dated before the date the product was first marketed. There are no restrictions on the type of article (trial or review for example), nature of the trial (preclinical or clinical) or the quality of the review or study. Reference lists are searched for additional relevant papers.
  - Google internet search: The internet is searched using the various terms identified for the product. The aim of this search is, in particular, to identify review stories relating to the product including any “success stories” relating to academic developments.

Pubmed
Google

1.5 Funding information

3rd step: search for public project grants

nature & amount of funding

The sources listed in section 1.4 are used to look for indications of grants or funding mechanisms or researchers/research groups involved in the development and testing of the product. Where the involvement of a funding body is indicated, the database/website of the funding organisation will be searched for detailed information on the nature and amount of funding. It is expected that the following funding bodies listed will be relevant to many of the products (note: the funding organisations will not be searched if there is no indication from the sources in 1.4 that they provided funding):

several funding databases

- NIH-RePORTER-Database
- EU-funding (CORDIS, H2020)
- Innovative Medicines Initiative (IMI)
- Army Grants
- European & Developing Countries Clinical Trials Partnership (EDCTP)
- National funding organisations where mentioned such as Medical Research Council (UK), Welcome Trust (UK), CNRS (France), BMBF (Germany) …
- Philanthropic organisations such as Bill & Melinda Gates Foundation.
- Others as determined by the search results …

1.6 References

[1] Cleary E. et al, Contribution of NIH funding to new drug approvals 2010-2016. www.pnas.org/cgi/doi/10.1073/pnas.1715368115.

[2] European Medicines agency. Human medicines highlights 2017. https://www.ema.europa.eu/en/documents/report/human-medicines-highlights-2017_en.pdf.

[3] Head M. et al, UK investments in global infectious disease research 1997-2010: a case study. Lancet Infect Dis 2013; 13: 55-64.

[4] Schuhmacher A. Changing R&D models in research-based pharmaceutical companies. Journal of Translational Medicine 2016; 14: 105

[5] Stevens A. et al, The role of pubic-sector research in the discovery of drugs and vaccines. NEJM 2011; 364(6): 563-541.

2 Case Studies

The detailed results are summarized in an excel-database.
They can be provided on request.

2.1 Nusinersen (Spinraza®): Summary of results

Background

The aim of this piece of research was to identify the non-industry-financed component of R&D activities in the development of Spinraza® (a product for treating children and adults with spinal muscular atrophy (SMA), marketed by Biogen. The focus on the research is on project funding through public funding bodies and contributions from philanthropic/charitable organisations. We attempted to ascertain the level of funding using bibliographic and/or website sources. No qualitative methods were used. Not included are tax concessions on costs arising from any research activities carried out by the pharmaceutical company.

product for spinal muscular atrophy/SMA

funding information from bibliographic and/or website sources

Methods

The methods outlined above were followed. Not included in the methods: estimation of amount of tax deductions (orphan drug tax credit or priority review voucher). Method strategies were developed in an iterative process following exchanges of ideas between international researches in regular web conferences. Research activities generally also continue beyond the date of market authorization, which cannot therefore be attributed to *development* costs. We therefore used 2017 as the cut-off date for potentially relevant projects and funding. We identified 2007 as the relevant year for product-specific development. According to the National Institute of Neurological Disorders and Stroke (NINDS) timeline document, this was the time point at which researchers first described the antisense oligonucleotides that were to become nusinersen.

methods as outlined:
not included:
estimation of amount of tax deductions

2007-2017
as cut-off dates

Results

Particularly useful databases regarding the identification of projects researching SMA therapies was “Orphanet”. Regarding funding information, the NIH (via the NIH reporter database) and the Canadian Institutes of Health Research (CIHR) as well as from the charity side, the Muscular Dystrophy Association (MDA), provided detailed information on the level for funding provided for projects they supported. The NINDS timeline document that detailed NINDS/NIH support for product development (identified through the google search) was a useful source. The 10-k report identified via the US Securities and Exchange Commission Filings was also helpful in identifying patent numbers related to the product, which enabled further searching in the Orange Book and patent databases. Through Pubmed only 1 additional project was identified (from a total of 11 hits generated up to market approval date) that had not already been identified through other sources.

Sources:

Orphanet,
CIHR
MDA
NIH reporter Db
Orange Book
Patent Db

National/international funding bodies

CIMR: 6 projects

- 6 projects funded by Canadian Institute of Health Research (CIMR) for a total of Can $ 3,269,130.

NIGMS, NINDS: 3 projects

2 researchers: 7 projects

- 3 National Institute of General Medical Sciences (NIGMS) or National Institute of Neurological Disorders and Stroke (NINDS) for a total of US $ 11,117,535 plus an additional 7 projects conducted by the 2 main researchers named in the patent projects for an additional $ 11,136,414.

E-Rare EU: 1 project

- E-Rare EU calls 1 project funded (amount not given).

BMBF: 1 project
DFG: 1 project

- 1 BMBF (German national funding programme) funded project € 387,854; 1 project was co-funded by the Deutsche Forschungsgesellschaft (DFG, no information on funding amount available).

European Funding bodies (IT, F): several projects

- Other national European funding bodies: Italian (Fondazione Telethon: 2 projects) and French (Association Franfaise contre les Myopathies, the Actions Concertees-Science du Vivant, the Institut Electricite Sante, the Groupement de Recherches et d'Etudes sur les Genomes and the Programme Hospitalier de Recherche Clinique) national funding, although no funding amounts could be identified on the websites of these organisations.

Charity funding

MDA: several projects

- Details could be found on 15 Muscular Dystrophy Association (MDA) funded projects totalling $ 3,768,516. On the MDA website it is claimed that MDA has invested more than $ 45 million in SMA research

Families of SMA

Cure SMA

- Families of SMA/Cure SMA (USA) was involved in supporting 4 projects and Kids' Cures in 1 project. Here the exact funding amount is unavailable. 1 project funded by Families of SMA amounted to $ 381,138.

SMA Europe

- It is stated in the Cure SMA annual report, that funding for research projects in 2018 totalled 5 million US $ (on various Cure SMA website postings, specific projects totalling 1 Million US $ are detailed, together with the names of the recipients).

SMA Foundation

- SMA Europe lists a number of projects funded in this area before the date of market authorization (although there is no description of the projects, which makes an exact assignment to the medication impossible); these total just over € 3 Million.
- According to its website, the Spinal Muscular Atrophy Foundation (SMA Foundation) has spent around $ 150 Million on basic, translational and clinical research since its inception in 2003.

Final figure

€ 165 million public research funding (including charities)

Converting all monetary amounts into a common Euro currency, leads to a total funding of estimate of around € 165 Million for research into therapies for SMA. Taking a very conservative approach, i.e. just including projects named in the patents (or conducted by the same researchers named in the patents) or named specifically in development documents, around just over € 20 Million can be directly attributable to Spinraza®.

Conclusions

The NINDS timeline document provided an overview of the period of drug development and was a useful background reference. Through patents and the NINDS timeline document, a number of NIH-funded research projects could be identified. Charitable and philanthropic organisations often named a total figure invested in research into therapies for SMA. To what extent these can be attributed to the development of *specific* pharmaceuticals (as opposed to basic research, which can be used for the development of *all* pharmaceuticals in this area) is difficult to estimate. For instance there are now two pharmaceutical products that have been developed for SMA which will have both used the results of basic research (at the time of writing, information that the new SMA treatment from Novartis "Zolgensma" – likely to be the world's highest price for a single treatment– has received approved by the FDA, hit the headlines)[3].

NINDS timeline document: valuable source!

difficult to distinguish basic research and product development research

2.2 Cerliponase alpha (Brineura®): Summary of results

Background

The aim of this case study was to identify the non-industry-financed component of R&D activities in the development of Cerliponase alfa (international nonproprietary name), marketed internationally as Brineura® by the pharmaceutical company BioMarin. Cerliponase alfa is an enzyme replacement therapy (ERT) that delivers TPP1 directly to the brain of children with Neuronale Ceroid-Lipofuszinosen (CLN2) disease and is approved to slow the loss of walking or crawling ability in children with CLN2 disease who are three years of age and older. The focus of this research is on identifying project funding through public funding bodies and contributions from philanthropic/charitable organisations. As before, we attempted to ascertain the level of funding using bibliographic and/or website sources. No qualitative methods were used. Not included are tax concessions on costs arising from any research activities carried out by the pharmaceutical company.

product for enzyme replacement therapy/ERT for CLN2 disease

funding information from bibliographic and/or website sources

Methods

The methods outlined above were followed. Not included in the methods: estimation of amount of tax deductions (orphan drug tax credit or priority review voucher). Research activities generally also continue beyond the date of market authorization, which cannot be attributed to *development* costs. We therefore used 2017 as the cut-off date for potentially relevant projects and funding. As the beginning of product-specific development we identified 2000 as the relevant year. According to the National Institute of Neurological Disorders and Stroke (NINDS) timeline document, this was the time point at which researchers first isolated TPP1 successfully to produce recombinant TPP1 in a cell culture system.

methods as outlined:
not included:
estimation of amount of tax deductions

2000-2017 as cut-off dates

[3] https://www.nytimes.com/2019/05/24/health/zolgensma-gene-therapy-drug.html

Results

Sources:

NIH reporter Db little charity information

The NINDS timeline document that detailed NINDS/NIH support for product development (identified through the google search) was a useful source of project information, as was PubMed. The search for information on public disclosures from patent documents identified several NIH projects, as did searching the NIH Reporter database using the names of key principal investigators. The information from charities regarding funding was however not as informative as with the Spinraza® case study; as a result we were unable to estimate the monetary contribution from charitable organisations.

National/international funding bodies

NIH: 13 projects

- 13 National Institute for Health (NHI) research projects were identified, for a total of US $ 28,775,650.

NSF: 1 project

- The US National Science Foundation (NSF) funded a project to the amount of $ 94,931.

AKA: 1 project

BMBF: 3 projects

- In terms of European national funding, 1 relevant project was identified as being funded by the Academy of Finland (AKA) (€ 740,120) and 1 by the German Ministry for Education and Research (BMBF) (€ 390,457). For 2 BMBF funded projects we could find no information on the funding amount.

EU-FP7: 1 project

- The European Union Seventh Framework Programme (FP7/2007-2013) funded the DEM-Child project which had an overall budget of € 3,971,420.

Charity funding

BDSRA

no further information

- The Batten Disease Support and Research Organisation (BDSRA) lists some information on projects and project fundings (but by no means all) on their website or in some of the annual reports. Here an amount of US $ 297,391 could be identified, that specifically went into the development of treatments for CLN2.
- For the Neuronale Ceroid-Lipofuszinose (NCL) Stiftung, BDFA UK, Beyond Batten Disease Foundation, Charlotte & Hwenyth Gray Foundation: no projects or funding amounts could be identified for CNL2.

Final figure

NOT possible to estimate a total CNL2 funding amount that includes funding from charities

It was not possible to estimate a total CNL2 funding amount including charitable and philanthropic organisations as there was too little transparent information available online regarding charitable funding. Taking a very conservative approach, i.e. just including projects named in the patents (or conducted by the same researchers named in the patents) or named specifically in development documents, around just over 31 Million Euros can be directly attributable to Brineura® through public funding.

Conclusions

several national and international publically-funded projects identified with funding amounts + projects from charities, but no concrete figures identified

The NINDS timeline document provided an overview of the period of drug development and was a useful background reference. Through patents and the NINDS timeline document, a number of NIH-funded research projects could be identified. Charitable and philanthropic organisations did not often name a total figure invested in research into therapies for CLN2, added to which Batten Disease is comprised of a number of distinct CNL diseases which made attribution of specific charitable contributions to therapies for the disease in question difficult.

2.3 Burosumab (Crysvita®): Summary of results

Background

The aim of this case study was to identify the non-industry-financed component of R&D activities in the development of Burosumab, marketed internationally as Crysvita® by the pharmaceutical company Kyowa Kirin. Burosumab is a monoclonal antibody that blocks X-Linked Hypophosphatemia (XLH) and is approved to treat children with a disorder of FGF23. The focus of this research is on identifying project funding through public funding bodies and contributions from philanthropic/charitable organisations. We attempted to ascertain the level of funding using bibliographic and/or website sources. No qualitative methods were used. Not included are tax concessions on costs arising from any research activities carried out by the pharmaceutical company.

product for children with a disorder of FGF23

funding information from bibliographic and/or website sources

Methods

The methods outlined above were followed. As previously described, these methods were developed in an iterative process, in part following the exchange of ideas between international researches working in this area. Research activities generally continue beyond the date of market authorization, which cannot therefore by definition be attributed to development costs. We used 2017 (date of EMA market authorization) as the cut-off date for potentially relevant projects and funding. We identified 1995 as the relevant year from which date research could be considered to be directly product related. According to a review article (Carpenter, 2012), a phosphate-regulating gene with homology to endopeptidases on the X chromosome (PHEX) was identified in the 1990s as the mutated gene in XLH; the reference given for this discovery was a publication by Francis in 1995, hence this was taken as the relevant year. As the first results were to show, direct product development appeared to take place within Japan using Japanese public funding, details of which we were not able to find details in English. Therefore, we decided to include funding into the development and testing of animal models that took place *after 1995* and directly enabled drug development to take place. It is important to note, that this basic science cannot readily be wholly and directly attributed to a specific drug. However, since we were developing and testing basic methodological research regarding whether public funding can be traced, the results of this case study also provides interesting, as yet undocumented information.

methods as outlined:
not included:
estimation of amount of tax deductions

1995-2017 as cut-off dates

mostly Japanese public research funding

no English-language sources on this funding

public funding of basic research after gene identification was included

Results

National/international funding bodies

- 3 NIH projects were identified by the Orphanet databasetotalling US $ 2,129,108.
- The PubMed search specifically for animal models revealed a further NIH project with funding going to the Universities of Tennessee and Kansas and Duke University, totaling US $5,476,755 over 16 yearsas well as 7 other NIH projects, that were identified as relevant from the PubMed search, with a total funding of US $ 20,541,065.
- A key investigator search on NIH reporter revealed 2 further relevant projects within the specified time period totalling US $ 3,157,908.

NIH (USA):
13 projects

NIH (USA): ca. US $ 25 Million

- In total, therefore, NIH funding of basic research to the value of US $ 25,828,081 was identified.

Japanese national funding

- 1 Patent and 3 pubmed publications (Aono et al, 2009; Shimada et al, 2004; Yamazaki et al, 2008) referred to diverse projects that had received grants from the Ministry of Education, Culture, Sports, Science and Technology of Japan and from the Ministry of Health, Labor and Welfare of Japan as well as the Japan Society for the Promotion of Science. It was not however possible to ascertain funding amounts for these projects.
- The Japan Foundation for Pediatric Research was named in 1 publication (Kawai et al, 2013) identified via the Pubmed search but no funding information was found. Grants-in-Aid for Scientific Research from the Japanese Society for the Promotion of Science were involved in the funding of the work by Miyagawa; here a database of research projects was available in English but without funding amounts specified.

other national funding programmes

- Project funding by the Austrian Science Fund € 423,832.50 awarded to Reinhold Erben between 2011 and 2016 was identified via the pharmaceutical company's website.

AT, CA, S

- Genome Canada and the Ontario Genomic Institute as well as the Canadian Institutes of Health Research, Centre for Modeling Human Disease grant were named in Owen (2012), however no funding details could be found. A Canadian Institutes of Health Research funded project was identified to the value of Can $ 709,152 (Larsson, 2014).
- The Swedish Research Council and Swedish Society of Medicine part funded the work by Larsson.

Charitable funding

several projects from charities were identified, but no concrete figures on funding

- The Ralph W & Grace M Showalter Research Trust Fund part-funded research work as noted in the publication by Clinkenbeard (2016). The Showalter Research Trust was also named in the funding of the work published by Farrow et al (2010) and Ichikawa et al (2012).
- An American Heart Association Postdoctoral Fellowship was referred to (Clinkenbeard, 2016) as was a European Society for Paediatric Endocrinology Research Fellowship (Liu, 2016).
- The National Kidney Foundation was involved in funding the work by Farrow.
- The Indiana Genomics Initiative (Clinkenbeard, Farrow) and the Indiana University School of Medicine (Ischikawa) were named as further sponsors; no further details are available on these sponsors/awards.

Final figure

only possible to base estimate on NIH information: ca. € 26,800,000

Converting all monetary amounts into a common Euro currency leads to a total funding estimate of around € 26,800,000 for research into therapy development related to Burosumab. The bulk of the known, specified funding was from the NIH (here we only included basic research that took place *after* the relevant mutated XLH gene had been discovered); details into the often cited contribution of Japanese sources to product development could not be ascertained.

Conclusions

Funding related directly to drug development was listed in several instances as coming from Japan, however it was not possible to identify English language details related to this funding. The research identified, for which project and funding information was documented, was more concentrated on basic research once the mutated gene in XLH had been discovered, which is a necessary precursor to drug therapy development.

little transparency with Japanese sources was found

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